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RESEARCH

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Sirtuin-1 level and gene polymorphisms in multiple sclerosis

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Abstract

Background Sirtuin-1 (SIRT1) may affect multiple sclerosis (MS) disease. This study aimed to investigate the level of serum SIRT1, mRNA expression and genetic polymorphisms in Egyptian MS sufferers. Also, to assess its role as a possible biomarker in predicting the risk of MS and to evaluate the association between its levels and disability of MS. Measurement of SIRT1, serum level, mRNA expression level and genotyping for sirtuin-1 gene polymorphisms in 240 Egyptian subjects; 120 MS sufferers and 120 healthy control subjects.

Results There was a significant diminishment of level of serum sirtuin-1, and sirtuin-1 mRNA expression in MS sufferers compared to control subjects. Different sirtuin-1 single nucleotide polymorphism frequencies were statistically significant in MS sufferers compared to the control subjects. Moreover, a negative correlation of serum level of sirtuin-1 in MS sufferers with MS disease duration, disability according to Expanded Disability Status Scale (EDSS) score, cholesterol, and triglyceride serum levels. Regarding the sirtuin-1 gene polymorphisms in MS sufferers, the rs7895833 GG genotype had significant higher cholesterol, and low-density lipoprotein (LDL) levels than the GA and AA genotypes and that the rs7069102 GG genotype had a higher LDL level than the CG and CC genotypes while the rs2273773 TT genotype was significantly associated with cholesterol, and LDL levels than the TC and CC genotypes. No significant difference was detected in EDSS score comparing different sirtuin-1 genotypes among MS sufferers. In MS sufferers, rs7895833 G allele can be independently associated with cholesterol, triglycerides, and LDL levels. rs7069102 C allele can be independently associated with LDL level. With regard to rs2273773, T allele, it can be independently associated with cholesterol and LDL levels.

Conclusion There was a significant association between different sirtuin-1 gene polymorphisms and dyslipidemia which may modulate the course of MS disease. Furthermore, serum sirtuin-1 level can be considered as a possible predictor of disability in multiple sclerosis sufferers.

Keywords Sirtuin, Serum level, Genetic variant, Multiple sclerosis

Background

The sirtuin 1 gene, located on the 10q21.3 chromosome [1], considered as a member of a histone deacetylases family that target transcription factors, histones and coregulators to adapt expression of gene to the cellular energy state [2] by reversing acetylation of histone proteins that organize transcription factors such as nuclear factor-κB (NF-κB), and p53 [3].

Sirtuin 1 that is found in brain, skeletal muscle, pancreas, liver and adipose tissue [4] has great effect on DNA stability, acts as barrier to protect cells against oxidative stress and modifies energy metabolism, DNA repair, as well as the response to oxidative damage [2].

The activity of sirtuin 1 (SIRT1) is dependent on nicotinamide adenine dinucleotide that affects electronic transmission of mitochondria, cellular oxygen supply, cell activation, inflammation and atherosclerosis. Antioxidant can downregulate these pathways [5].

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Sirtuin 1 has been linked to neurodegenerative disease, inflammation, cardiovascular diseases, and amyotrophic lateral sclerosis. Moreover, it is a potential therapy for amyotrophic lateral sclerosis [4].

Given that there might be no previous reports which discussed the association between genetic variants and level of SIRT1 in multiple sclerosis sufferers in Egypt, the current study aimed to investigate SIRT1 serum level, mRNA expression level and genetic polymorphisms (rs7069102 C > G, rs7895833 A > G and rs2273773 C > T) in Egyptian patients with multiple sclerosis.

Methods

The present study is a case–control study that was conducted from January 2021 to January 2022 on 240 Egyptian subjects; 120 clinically defined MS sufferers recruited from MS unit, Neurology department in our university hospitals. 120 healthy control subjects (they did not suffer from hypertension, liver or renal diseases) matched for age, and sex with MS sufferers' group were recruited from the outpatient clinics during the same period of the study and included in this study. MS sufferers and control subjects assigned an informed written consent.

All clinically defined multiple sclerosis sufferers according to the McDonald criteria of 2017 [6] were eligible for the current study. We omitted MS sufferers with a history of autoimmune disorders, vascular disease, intracranial or intraspinal tumor, antihormonal therapy, exacerbations in the month before the study, steroids for one month prior to study enrollment, active acute or chronic infections, use of antibiotics in the last month, participants refused to give an informed written consent.

Participants of this study underwent complete medical history taking (with special emphasis on the date of onset of multiple sclerosis, duration of the disease, and type of MS), full general and neurological examinations. We assessed the clinical disability of multiple sclerosis group by using the Kurtzke Expanded Disability Status Scale (EDSS) score. It provides a total score on a scale ranging from zero to ten (from normal examination to death from multiple sclerosis, respectively) [7]. Magnetic resonance imaging of the brain and spine was conducted by using one and half Tesla Philips superconducting magnetic resonance imager with a standard head coil.

Fresh blood samples were collected from all included subjects under complete aseptic condition, divided into three parts: the first part of fresh blood was collected in heparin containing vacutainer used for isolation of peripheral blood mononuclear cells (PBMCs). We collected the second part into EDTA containing vacutainer for DNA extraction. And the third part was collected into plain vacutainer for serum separation and estimation of SIRT 1 serum level and lipid profile.

Quantitative measurement of SIRT1 level was determined using a commercially available ELISA assay purchased from thermofisher.com (Catalog NO. EH427RB), following the instructions of manufacturer.

Peripheral blood mononuclear cells were separated from peripheral blood by standard density-gradient centrifugation using lymphocyte separation medium (Ficoll). In brief, blood was diluted one: three with sterile phosphate buffered saline then became layered over the separating medium then centrifuged at 2000 rpm for 20 minutes. PBMCs layer were carefully aspirated after centrifugation. Extraction of RNA and reverse transcription was done in the same day.

Extraction of genomic DNA from whole blood: using the commercially available G-spin TM Total DNA Extraction Kit (iNtRON Biotechnology, Seongnam, Korea). The extracted DNA was detected by submarine agarose gel electrophoresis and visualized on ultraviolet transilluminator (Fig. 1). We determined purity and concentration of DNA spectrophotometrically at 260 and 280 nm. The purified genomic DNA was stored at − 20 °C until use. Genotyping of rs7895833 A > G, rs7069102 C > G and rs2273773 C > T polymorphism in SIRT1 gene polymorphism was achieved using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA; for rs7895833 A > G SNP Assay ID C_29163689_10 was used, for rs7069102 SNP Assay ID C_1340389_10, for rs2273773 C > T SNP Assay ID C_16179813_10 Thermo Scientific, Waltham, MA, USA).

Total RNA extraction from PBMC, and complementary DNA (cDNA) synthesis: total RNA was isolated according to RNA isolation kit (Gentra, Minneapolis, MN 55441 USA) following the manufacturer's protocol. We monitored total RNA purity and integrity by the absorbance of ultraviolet light spectrophotometrically at 260/280 nm. For the synthesis of cDNA, reverse transcription of the extracted RNA was performed by QuantiTect SYBR Green reverse transcription

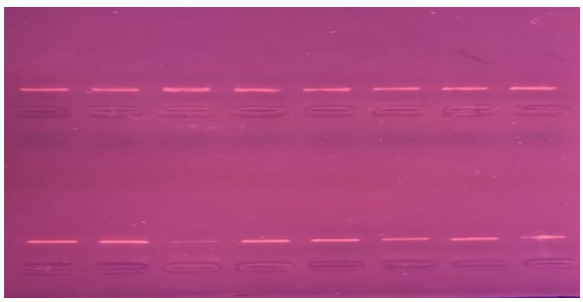


Fig. 1 Extracted DNA

(RT–PCR) kit (Qiagen; catalog no.204243) as recommended by the manufacturer. Complementary DNA was detected by agarose gel electrophoresis (Fig. 2) and stored at − 20 °C until time of analysis.

Level of SIRT1 mRNA expression were estimated by real time polymerase chain reaction using Step One TM System (Applied Biosystems). We used glyceraldehyde-3-phosphate dehydrogenase gene (G3PDH) as an internal control. Primers sequence for SIRT1 gene were (For: 5′-TGGCAAAGGAGCAGATTAGTAG-3′, Rev: 5′-GGCATGTCCCACTATCACTGT-3′). The PCR was performed in 25 µL containing 12.5 µL QuantiFast SYBR Green (Cat.No.204141), PCR Master Mix, 1 µL of each primer (Invitrogen, USA) and 2 µL cDNA.

The thermal cycling profile was an initial denaturation at 95 °C for two minutes followed by 40 cycles of denaturation at 94 °C for 30 s, annealing at 52 °C for 60 s and the elongation at 72 °C for 2 s for 40 cycles with a final incubation at 72 °C for seven min. All genes expression was reported as the D cycle threshold (DCt) value. Expression levels of mRNAs for target genes were compared with endogenous control β-actin using the $2-\Delta\Delta CT$ method. All kits were supplied by QIAGEN (Valencia, CA).

Statistical analysis

Variables of this study are expressed as means ± SD for continuous data, and as numbers and percentages for categorical data. Student's "*t*" tests, Chi-square test, one-way analysis of variance, Mann–Whitney tests, Kruskal–Wallis, Spearman's correlation coefficient (*r*), multiple logistic regression analysis, and linear regression analysis were done when appropriate in the current study. Values of *p* less than 0.001, 0.05 in this study were considered statistically highly significant and significant, respectively. We carried out statistical computations using the statistical package of social science program for Windows version 24 that is released 2016 by International Business Machines Corporation, USA.

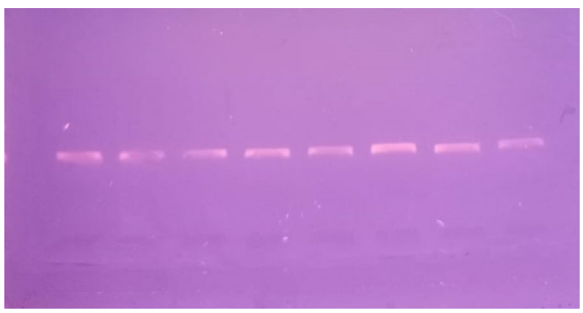


Fig. 2 Complementary DNA

Results

In the current study, 58% of MS sufferers' group were females, 42% were males and their age ranged from 18 to 45 years with a mean age (± SD) was 37.5 (± 5.5) years. While 55% of the control subjects were females and 45% were males with a mean age (± SD) was 36.05 (± 5.46) years. The mean age (± SD) at onset of MS was 26.31 ± 7.86 years and the mean MS disease duration (± SD) was 4.61 ± 3.33 years. There was significant difference in serum level of SIRT1 between control subjects and MS sufferers ($p < 0.0001$) (Table 1).

The sensitivity and specificity of serum SIRT1 as a diagnostic marker in multiple sclerosis was also assessed by a receiver operating characteristic (ROC) curve (Fig. 3). We found a significant serum SIRT1 cutoff for MS was < 2.4 ng/mL with a sensitivity of 78% and a specificity of 68.52%, positive predictive value of 63.5%, negative predictive value of 68.6%, AUC was 0.724 and *P* value was 0.03.

mRNA expression of SIRT1 was significantly decreased in MS sufferers when compared to control subjects (Fig. 4).

The frequencies of genotypes and alleles in sirtuin 1 gene among MS sufferers and control subjects are shown in Table 2. CC, TC and TT genotype frequencies of rs2273773 were 40%, 38% and 22%, respectively, in MS sufferers, and these were 52%, 40% and 8%, respectively, in controls ($P=0.01$). While the frequencies of C and T alleles among MS sufferers were 58% and 42%, respectively, these were 75% and 25%, respectively, in control subjects ($P=0.006$). GG, AG and AA genotype frequencies of rs7895833 were 45%, 28% and 27%, respectively, in MS sufferers, and these were 25%, 25% and 50%, respectively, in control individuals ($P=0.0004$). While the frequencies of G and A alleles in MS sufferers were 60% and 40%, respectively, these were 40% and 60%, respectively, in control individuals ($P=0.002$). GG, CG and CC genotype frequencies of rs7069102 were 52%, 28% and 20%, respectively, in MS sufferers, and these were 25%, 27% and 48%, respectively, in control subjects ($P<0.00001$). The frequencies of G and C alleles among MS sufferers were 65% and 35%, respectively, on the other hand in control subjects these were 45% and 55%, respectively ($P=0.002$).

There was a significant negative correlation between the serum level of SIRT1 and the duration of MS disease ($r=-0.39$, $p=0.03$), Expanded Disability Status Scale score ($r=-0.38$, $p=0.01$), cholesterol level ($r=-0.36$, $p=0.01$) and triglycerides levels ($r=-0.44$, $p=0.003$) among MS sufferers (Table 3).

There was a significant relation of SIRT1 rs7895833 GG with higher cholesterol ($P=0.04$) and low-density lipoprotein levels ($P=0.001$). SIRT1 rs7069102 GG genotype

Table 1 Demographic and biochemical data of MS sufferers and control subjects

	MS sufferers	Control subjects	*P* value
Age (years)	37.5 ± 5.5	36.05 ± 5.46	0.14
Sex			
Female	70 (58%)	66 (55%)	0.7
Male	50 (42%)	54 (45%)	
Disease duration (years)	4.61 ± 3.33	–	–
Mean age at onset of MS	26.31 ± 7.86	–	–
Expanded Disability Status Scale	2.34 ± 1.33	–	–
Disease course			
Relapsing–remitting	90 (75%)	–	–
Progressive	30 (25%)		
Total cholesterol (mg/dL)	189 ± 38 180 ± 43 0.37	180 ± 43	0.08
Low-density lipoprotein (mg/dL)	86 ± 29	80 ± 27	0.09
High-density lipoprotein (mg/dL)	52 ± 5	53 ± 5	0.1
Triglycerides (mg/dL)	85 ± 22	79 ± 28	0.06
Serum SIRT1 level (ng/ml)	2.1 ± 0.25	3.4 ± 0.2	< 0.0001**

MS multiple sclerosis, *SIRT1* Sirtuin1

**$p < 0.001$: highly statistically significant

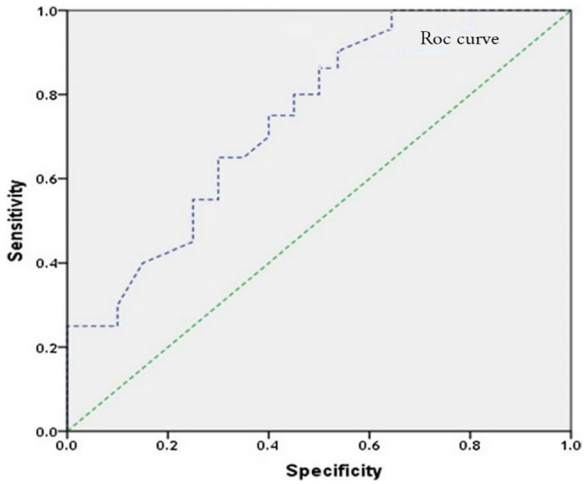


Fig. 3 Receiver operating characteristic (ROC) curve of serum sirtuin-1 as a diagnostic marker in multiple sclerosis

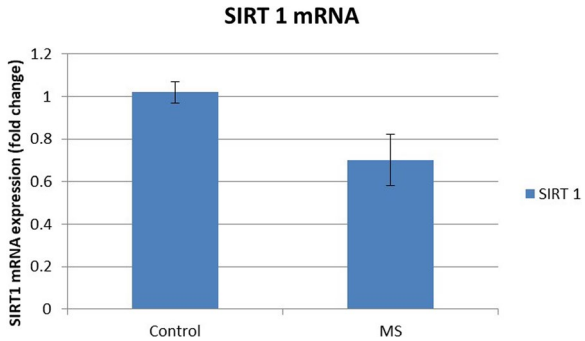


Fig. 4 SIRT1 mRNA expression in the studied groups

was associated with higher low-density lipoprotein level ($P=0.02$). SIRT1 rs2273773 TT genotype was significantly associated with higher cholesterol ($P=0.04$) and low-density lipoprotein levels ($P=0.002$) (Table 4).

No significant difference was detected in Expanded Disability Status Scale score comparing different SIRT1 genotypes among MS sufferers (Fig. 5a–c).

Table 5 shows linear regression analysis of different SIRT1 gene polymorphisms (rs2273773, rs7069102 and rs7895833) with clinical and laboratory parameters among MS sufferers. For SIRT1 (rs7895833), G allele can be independently associated with higher cholesterol ($P=0.04$), triglycerides ($P=0.02$), and low-density lipoprotein levels (0.03). For SIRT1 (rs7069102), G allele can be independently associated with higher low-density lipoprotein level ($P=0.04$). With regard to SIRT1 (rs2273773), T allele can be independently associated with higher cholesterol ($P=0.03$) and low-density lipoprotein levels ($P=0.01$).

Discussion

Sirtuin-1 gene has a significant role in production of pro-inflammatory cytokines, regulates transcription factors, DNA repair factor Ku70 and the transcriptional coactivator p300 [3, 8]. Therefore, a broad range of cellular processes including cell survival and inflammation are under the control of SIRT1 [9]. SIRT1 has an anti-inflammatory activity as SIRT1 inhibits transcription of NF-κB which also inhibits SIRT1 activation [10].

Moreover, immune cells are involved in regulating the expression of sirtuin and the pathogenesis of multiple

Table 2 Distribution of SIRT1 genetic variants and allelic frequency among MS sufferers and control subjects

Variables			MS sufferers		Control subjects		95% CI	OR	*P*-value
			No	%	No	%			
rs2273773	Genotype	CC	48	40	62	52	0.37–2.24	1.35	0.01*
		CT	46	38	48	40	0.67–8.94	1.41	
		TT	26	22	10	8	1.94–3.73	3.83	
	Allele	C	70	58	90	75	0.43–5.52	3.86	0.006**
		T	50	42	30	25	1.48–2.27	1.41	
rs7895833	Genotype	GG	54	45	30	25	2.56–5.75	2.48	0.0004**
		AG	34	28	30	25	0.56–2.75	5.49	
		AA	32	27	60	50	0.61–11.91	1.49	
	Allele	G	72	60	48	40	1.91–3.71	3.98	0.002**
		A	48	40	72	60	0.47–2.22	1.01	
rs7069102	Genotype	CC	24	20	58	48	0.91–3.71	1.88	< 0.00001**
		CG	34	28	32	27	0.33–6.51	1.93	
		GG	62	52	30	25	1.93–3.70	2.85	
	Allele	C	42	35	66	55	0.49–2.23	1.04	0.002**
		G	78	65	54	45	1.73–3.94	3.38	

MS multiple sclerosis, *SIRT1* Sirtuin1, *OR* odds ratio, *CI* confidence interval

* Statistically significant; **highly statistically significant

Table 3 Spearman correlation coefficient of serum SIRT1 level with other factors among MS sufferers

Variables	*R*	*P* value
Age (years)	0.07	0.59
MS disease duration	−0.39	0.03*
Expanded Disability Status Scale score	−0.38	0.01*
Cholesterol level (mg/dL)	−0.36	0.01*
Triglycerides level (mg/dL)	−0.44	0.003**
Low-density lipoprotein level (mg/dL)	−0.25	0.12
High-density lipoprotein level (mg/dL)	0.28	0.06

MS multiple sclerosis, *SIRT1* Sirtuin1

* Statistically significant; **highly statistically significant

sclerosis, but they are poorly studied. Th17 cell is an important component of the adaptive immune system that is involved in the pathogenesis of most autoimmune and inflammatory syndromes. SIRT1 increases the transcriptional activity of RORgt which is the hallmark transcription factor of Th17 cells. SIRT1 enhances Th17 cell production and function [11].

Therefore, we planned to investigate the SIRT1 serum level, expression level and genetic polymorphisms (rs7069102 C > G, rs7895833 A > G and rs2273773 C > T) among Egyptian MS sufferers.

We found a significant serum SIRT1 cutoff for MS was < 2.4 ng/mL with a sensitivity of 78% and a specificity of 68.52%, positive predictive value of 63.5%, negative predictive value of 68.6%, and AUC was 0.724.

To assess the impact of SIRT1 on the pathogenesis of MS, in the current investigation, there was significant decrease in SIRT1 serum level in MS sufferers when compared to control subjects. Also, SIRT1 mRNA expression was considerably reduced in peripheral blood mononuclear cells of MS sufferers.

Previous researchers have declared similar findings. Tegla and colleagues [12] found that SIRT1 mRNA expression in brains and peripheral blood mononuclear cells obtained from sufferers with relapsing remitting multiple sclerosis was significantly decreased during relapse. It was found to be expressed in both acute and chronic brain lesions of multiple sclerosis sufferers by perivascular CD3 + and CD 68 +. Also, a remarkable increase in apoptosis after inhibition of SIRT1 expression was detected. Moreover, it has been identified as a probable biomarker of MS activity [12]. Hewes and colleagues [3] also found that during relapse of multiple sclerosis there was a statistically significant decrease in SIRT1 mRNA expression level in patients when compared to those in remission.

Also, Yang and colleagues [13] tested the effect of resveratrol on the SIRT1 levels, and an increased SIRT1 expression in peripheral blood mononuclear cells was found. Piotrzkowska and colleagues [14] observed that in patients with MS, there was a 1.8-fold decrease in the level of the SIRT1 gene expression compared to control group.

In our study, different genotype frequencies of SIRT1 single nucleotide polymorphisms (rs2273773, rs7895833

Table 4 Relation of different SIRT1 genotypes with demographic, clinical and laboratory parameters among MS sufferers

		Age (years)	Disease duration	Fasting blood glucose mg/dl	Cholesterol mg/dl	Triglycerides mg/dl	HDL mg/dl	LDL mg/dl
rs7895833	GG	28.8 ± 10.5	3.5 ± 1.1	120.2 ± 21.6	174.7 ± 33.1	175.8 ± 32.3	32.4 ± 10.7	122.5 ± 25.7
	GA	24.4 ± 10.3	3.7 ± 1.0	131.8 ± 15.4	133.9 ± 37.8	118.9 ± 39.8	38.2 ± 10.8	77.5 ± 34.5
	AA	21.0 ± 8.5	2.3 ± 1.0	126.6 ± 16.3	112.4 ± 22.6	113.8 ± 30.6	36.4 ± 9.1	57.8 ± 25.4
P value		0.4	0.13	0.5	0.04*	0.6	0.7	0.001**
rs7069102	GG	33.3 ± 11.2	3.2 ± 0.1	123.2 ± 16.4	171.2 ± 38.6	172.4 ± 36.4	33.7 ± 12.3	110.6 ± 27.8
	CG	24.2 ± 11.8	3.8 ± 0.3	128.8 ± 17.3	136.3 ± 41.4	118.6 ± 33.4	34.4 ± 8.8	66.2 ± 15.6
	CC	21.3 ± 11.6	3.3 ± 0.6	132.9 ± 17.0	142.2 ± 35.5	151.6 ± 29.0	31.7 ± 6.5	60.7 ± 23.1
P value		0.2	0.9	0.7	0.1	0.1	0.9	0.02*
rs2273773	TT	23.5 ± 11.8	3.1 ± 1.3	121.6 ± 17.0	149.1 ± 16.2	175.4 ± 37.3	36.0 ± 6.7	115.2 ± 25.4
	TC	22.3 ± 11.0	3.8 ± 1.5	132.9 ± 20.2	116.6 ± 14.3	123.2 ± 35.5	40.2 ± 6.5	70.8 ± 9.0
	CC	15.0 ± 6.2	2.0 ± 0.6	125.3 ± 11.6	128.3 ± 14.0	111.1 ± 39.0	40.1 ± 7.5	56.9 ± 11.7
P value		0.2	0.8	0.5	0.04*	0.09	0.5	0.002**

MS multiple sclerosis, *SIRT1* Sirtuin1, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

* Statistically significant; **highly statistically significant

and rs7069102) were statistically significant in MS sufferers' group compared to control subjects. With regard to rs2273773 polymorphism, we found that the T allele in MS sufferers was more prevalent than among control subjects and TT genotype was significantly associated with higher cholesterol and LDL levels than the TC and CC genotypes. Regarding the rs7895833 the G allele was more frequent in cases and GG genotype has a significant higher cholesterol, triglycerides and LDL than the GA and AA genotypes. Finally, according to rs7069102 the G allele was more prevalent in cases than in control individuals and the GG genotype has a higher LDL levels than the CG and GG genotypes. Furthermore, no significant difference was detected in Expanded Disability Status Scale score comparing different SIRT-1 genotypes among people with multiple sclerosis.

This finding was in accordance with the finding of another study carried out by Kilic and colleagues [15]. They found that the frequencies of mutant TT genotype for rs2273773 C > T in exon 5, were significantly higher in patients with cardiovascular disease as compared to healthy control subjects.

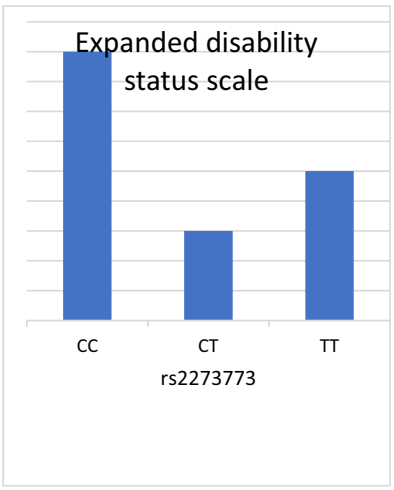
Elevated levels of circulating cholesterol and low-density lipoprotein are associated with adverse clinical and magnetic resonance imaging outcomes among the patients [16]. ApoB, the characteristic protein of LDL, was associated with greater CD80 + and CD19 + cell frequency in cerebrospinal fluid suggesting a possible role for the low-density lipoprotein compartment in promoting extravasation, proliferation or survival of CD80 + and CD19 + cells into the cerebrospinal fluid. CD80 + is a co-stimulatory molecule for T cell activation that is expressed on monocytes and activated B cells, whereas CD19 + is found on B cells. CD80 + cells and CD19 + cells are increased in peripheral blood mononuclear cells of multiple sclerosis sufferers [17].

In the same context Edgunlu and colleagues [18] found a significant difference between the rs2273773 polymorphism of SIRT1 gene among patients and control group ($p = 0.011$). Also, they found an association between MS disease and the haplotypes of rs7895833, rs7069102 and rs2273773 polymorphisms. They found that there was no association with Expanded Disability Status Scale score and rs7895833, rs7069102 and rs2273773 polymorphisms of the SIRT1 gene ($p > 0.05$).

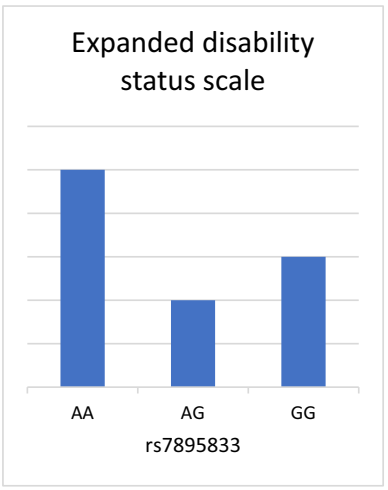
There was a significant negative correlation between serum SIRT1 level with disease duration, Expanded Disability Status Scale score, cholesterol level and triglycerides level. This finding met with that of Hewes and colleagues [3]. Ciriello and colleagues [19] suggested that phosphorylated SIRT1 levels correlate well with Expanded Disability Status Scale score in sufferers with early relapsing–remitting MS and no significant disability.

Conclusions

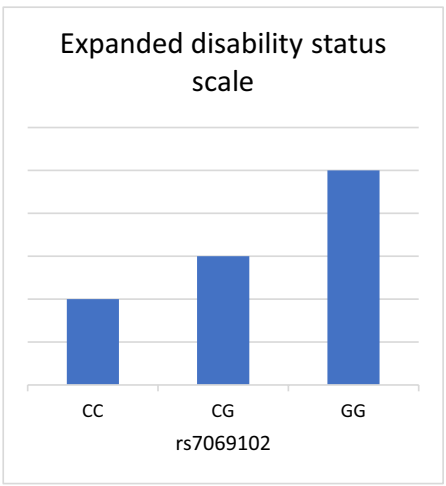
Sirtuin-1 polymorphisms may have a significant role in the development of multiple sclerosis. Significant association of SIRT1 polymorphisms with dyslipidemia that was detected in this study may modulate disease course in people with MS and can be considered as a potential diagnostic tool that would make therapeutic decisions easier, improving multiple sclerosis sufferers' quality of life. Moreover, this investigation opens new perspectives for the understanding of why lipids are altered at onset of MS disease and which pathways could be deregulated



a) Association of SIRT1 rs2273773 polymorphism and expanded disability status scale



b) Association of SIRT1 rs7895833 polymorphism and expanded disability status scale



c) Association of SIRT1 rs7069102 polymorphism and expanded disability status scale

Fig. 5 Association of different SIRT1 polymorphisms and Expanded Disability Status Scale in MS sufferers (**a**–**c**)

in multiple sclerosis diseases. Furthermore, serum SIRT1 level can be considered as a possible predictor of disability in people with MS. Further prospective studies are needed to concentrate on the other members of the SIRT family. Understanding the impact of SIRT1 on immune pathways is crucial to be able to design therapeutic strategies targeting SIRT1 in people with MS. In more prospective studies, the expression and mutations of SIRT1 gene should be analyzed with a larger group of MS sufferers. Also, the effect of drugs that activate SIRT1 and the effect of antioxidant on the activity of SIRT1 among MS sufferers should be analyzed.

Table 5 Linear regression analysis of different SIRT1 gene polymorphisms (rs2273773, rs7069102 and rs7895833) with clinical and laboratory parameters among MS sufferers

	SIRT1 genotypes					
	rs2273773		rs7069102		rs7895833	
	B	*P* value	*B*	*P* value	*B*	*P* value
Expanded Disability Status Scale	0.052	0.7	0.146	0.3	0.108	0.5
Disease duration	− 0.258	0.5	− 0.264	0.7	− 0.177	0.14
Fasting blood glucose (mg/dl)	0.055	0.6	0.144	0.1	0.107	0.4
Cholesterol (mg/dl)	− 0.336	0.03*	− 0.246	0.1	− 0.411	0.04*
Triglycerides (mg/dL)	− 0.285	0.06	− 0.205	0.2	− 0.356	0.02*
High-density lipoprotein (mg/dL)	0.131	0.4	0.011	0.9	0.127	0.4
Low-density lipoprotein (mg/dL)	− 0.397	0.01*	− 0.303	0.04*	− 0.525	0.03*

MS multiple sclerosis, *SIRT1* Sirtuin1

* Statistically significant

Abbreviations

MS	Multiple sclerosis
SIRT1	Sirtuin1
NF-κB	Nuclear factor-κB
HDACs	Histone deacetylases
EDSS	Expanded Disability Status Scale
PBMCs	Peripheral blood mononuclear cells
cDNA	Complementary DNA
G3PDH	Glyceraldehyde-3-phosphate dehydrogenase gene
DCt	D cycle threshold
r	Spearman's correlation coefficient
OR	Odds ratio
CI	Confidence interval
SD	Standard deviation
LDL	Low-density lipoprotein
HDL	High-density lipoprotein

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Author contributions
RSN, AF, MAA and AT carried out the work. RSN designed the study, collected the patients, gathered the clinical data, coordinated the research team, wrote the manuscript, had done the statistical analysis and reviewed the manuscript. AF, MAA and AT helped the laboratory work of the study and participated in the formal analysis. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final manuscript.

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Availability of data and materials
The corresponding author takes full responsibility for the data, has full access to all the data; and has the right to publish any and all data separate and apart from any sponsor.

Declarations

Ethics approval and consent to participate
The study was approved from the institute research board of Faculty of Medicine, Zagazig University, Egypt (ZU-IRB#6945/5-5-2021). A written informed consent was obtained from all the participants after informing them about the study rationale and their right to withdraw from the study at any time without any consequences.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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